Diagnostic imaging in Retinoblastoma

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CHAPTER 6

Summary
General discussion
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Retinoblastoma is a rare malignant disease occurring in very young children, which has a tremendous impact on visual prognosis. Nowadays, most children in Western countries survive their eye cancer, since tumors are usually detected while still confined to the anatomic margins of the eye. Over the past thirty years this has led to the implementation of effective local therapies such as laser- or crycoagulation, brachytherapy, thermochemotherapy and chemoreduction. These conservative treatment options have aided in avoiding the need for enucleation and external beam radiation in many patients (1). Newer techniques focusing on local application of chemotherapy, such as subconjunctival chemotherapy or selective intraarterial chemotherapy hold additional promise for treatment of patients with intraocular disease (2-4). All these conservative therapeutic options share the same drawback: since the eye is not enucleated there is no histopathologic gold standard to evaluate risk factors for local recurrence and metastatic disease. This makes accurate pretreatment imaging all the more crucial for local staging and treatment stratification.

The work presented in this thesis has centered on diagnostic imaging studies in retinoblastoma. Three different goals were set: (I) providing guidelines for imaging retinoblastoma, (II) investigating the value of magnetic resonance imaging (MRI) for assessment of both differential diagnosis and disease extent of retinoblastoma and (III), studying the capability of advanced MRI techniques for detection of retinoblastoma-related angiogenesis and tumor vitality.

DIAGNOSTIC IMAGING IN RETINOBLASTOMA

There are several reasons why MRI has won recognition in imaging eye tumors, surpassing computed tomography (CT). The advantages of MRI include lack of radiation exposure, higher spatial resolution, and higher soft tissue contrast. The potential diagnostic value of MRI is, however, highly dependent on the imaging protocol used (5). High-resolution MRI should be performed in patients suspected to have retinoblastoma, since small anatomic details must be assessed to determine the local extent of disease (optic nerve, choroid, sclera and anterior eye segment [AES]) (5-7). Hence, there is a need for a guideline for diagnostic imaging of retinoblastoma, including a standardized high-resolution MRI protocol. **Chapter 2.1** presents an overview of the current applications and limitations of imaging modalities for retinoblastoma and provides an MRI protocol for a state-of-the-art pre-treatment diagnostic evaluation of retinoblastoma patients. This study was carried out as part of the European Retinoblastoma Imaging Collaboration (ERIC), which is a group of radiologists from European retinoblastoma referral centers with an interest in undertaking collaborative studies using MRI methods in retinoblastoma.

VALUE IN DIFFERENTIAL DIAGNOSIS

Ophthalmologic examination in combination with ultrasound (under general anesthesia) serve as first-line diagnostic modalities and have a high diagnostic accuracy for diagnosing retinoblastoma. If the clinical diagnosis remains uncertain, MRI helps to characterize and differentiate intraocular abnormalities. This is especially the case when ophthalmologic evaluation is limited by opaque ocular refractive media, as may occur in many retinoblastoma simulating lesions. Two conditions that most commonly resemble retinoblastoma clinically are persistent hyperplastic primary vitreous (PHPV) and Coats disease (8). MRI can provide (sometimes subtle) additional information to narrow down the differential diagnosis. A smaller size of the affected eye in PHPV and Coats disease is thought to be a useful diagnostic parameter, since eye size in retinoblastoma is assumed to be normal (9-11). In **chapter 3.1**, we performed a retrospective analysis of MRI scans of 100 retinoblastoma patients (61 unilateral- and 39 bilateral patients), obtained ocular biometric data (axial length [AL], equatorial diameter [ED] and eye volume [EV]) and performed tumor volume measurements. In patients with proven unilateral retinoblastoma during follow-up, the contralateral normal eye was selected as a control. In our study, eyes with retinoblastoma had significantly shorter ALs and EDs, and significantly smaller EVs than normal eyes. A negative relationship between tumor volume and EV was found In patients with retinoblastoma. We eliminated possible confounding factors such as sex, age, and laterality, by using a multilevel regression model. Therefore, the use of eye size as a diagnostic parameter to differentiate between retinoblastoma and (benign) simulating lesions should be considered carefully, and a smaller eye size should not be used to exclude retinoblastoma or to favor a diagnosis of simulating lesions.
Dysplastic retinal tissue - a rare congenital defect - may also create a clinical and radiologic picture of an intraocular mass, closely resembling tumor tissue. MRI findings of a rare case of unilateral retinal dysplasia combined with optic nerve aplasia (**chapter 3.2**) are presented to facilitate discrimination of the more common causes of leukocoria.

DETECTION OF TUMOR EXTENT

The main role of pre-treatment MR imaging in retinoblastoma is to evaluate disease extent. Accurate staging of ocular neoplasms is increasingly important for the application of innovative vision-sparing treatments. In assessing the extent of the disease, MR imaging should include evaluation of intraocular tumor extension (AES, choroid, sclera, prelaminar optic nerve) as well as extraocular (postlaminar optic nerve and orbital invasion) or intracranial (primitive neuroectodermal tumor [PNET]

and metastases) tumor spread. Detection of optic nerve involvement is critical to determine the appropriate use of vision-sparing treatment modalities. Detection of extensive postlaminar optic nerve involvement is also important because these patients require preoperative neoadjuvant chemotherapy and subsequent surgical enucleation.

In **chapter 4.1** diagnostic accuracy of preoperatively performed MR imaging for the detection of disease extent was investigated in a large patient population with histopathologically proven retinoblastoma. MR images of 56 retinoblastoma patients (58 enucleated eyes), acquired on 1- or 1.5-T MRI scanners with a standard head coil were retrospectively analyzed. Demonstration of heterogeneous contrast enhancement and local thickening of the choroid adjacent to the tumor on contrast enhanced T1-weighted images showed a sensitivity of 73% for choroidal invasion, a specificity of 72% and accuracy of 72%. This imaging finding was characterized by a large number of false-positive findings. In these patients no delineation between enhancing choroid and tumor tissue was possible; this was probably due to partial-volume effects and lack of spatial resolution. Enhancement confined to a tumor that involves the (thickened) optic disc and interrupts linear enhancement of the choroidoretinal complex is very specific for tumor invasion of the prelaminar optic nerve. Prelaminar optic nerve involvement was detected with a sensitivity of 66% and a specificity of 96% and an accuracy of 79%. This imaging finding was characterized by a large number of false negatives, primarily caused by superficial (microscopic) infiltration of the optic nerve disk. Postlaminar involvement was correctly suspected in only 2 of 4 eyes; in two other eyes, this metastatic risk factor was missed. False positives for optic nerve involvement are also a problem with MRI because inflammatory change of the optic nerve or surrounding structures associated with tumor may sometimes be mistaken for optic nerve invasion. Choroidal inflammation combined with a granuloma in the optic nerve head may lead to an erroneous diagnosis, because the contrast enhancement pattern may mimic optic nerve invasion. In **chapter 4.2** we describe a case of unilateral retinoblastoma and false positive MRI findings of extensive optic nerve involvement, which was based on a combination of optic nerve inflammation and endothelial proliferation.

In previous reports, clinical tumor diameter and tumor thickness were proven to be predictive for optic nerve invasion but not for choroidal invasion (12;13). We found (**chapter 4.1**) a strong association between tumor volume and optic nerve involvement, but only for prelaminar invasion. This was probably due to the low incidence of postlaminar invasion in our study population. Tumor volume was also found to be an indirect radiological sign of choroidal invasion.

Midline PNET of either the suprasellar or the pineal region (pineoblastoma) are present in approximately 5%–15% of patients with hereditary retinoblastoma (14). Besides midline malignant tumors, benign intracranial abnormalities are reported in the retinoblastoma population. An increased incidence of pineal cysts in the hereditary subgroup was suggested in the literature (15;16). These cysts may mimic (early stage) pineoblastoma. Congenital brain anomalies and developmental anomalies have also been reported in patients with retinoblastoma, mostly in combination with 13q deletion syndrome (17;18). In **chapter 4.3** we retrospectively evaluated the presence of brain abnormalities on MR images in a group of 168 consecutive patients with retinoblastoma; 90 hereditary patients (54%), of which 7 patients had 13q deletion syndrome. Five pineoblastomas were detected, all in patients with hereditary retinoblastoma (5.5% in the hereditary subgroup). The total incidence of pineal cysts in our study was 5.4% (9 patients), with an incidence of 9.0% in the nonhereditary group (7 patients) and 2.2% in the hereditary group (2 patients). Structural brain abnormalities were restricted to the subgroup of patients with 13q deletion syndrome. From this study we concluded that pineoblastoma is associated with hereditary retinoblastoma, and structural brain abnormalities are restricted to patients with 13q deletion syndrome. Furthermore, the incidence of pineal cysts in retinoblastoma is similar to that in healthy children and is not associated with hereditary retinoblastoma. Small pineoblastomas, however, may have a cystic appearance, and the radiologist should be aware of this when analyzing pineal cysts in (hereditary) retinoblastoma patients.

RETINOBLASTOMA RELATED ANGIOGENESIS AND TUMOR VITALITY

Angiogenesis plays a key role in the pathogenesis of tumors. Without angiogenesis, solid tumors can not grow beyond 2 mm in diameter due to hypoxia; angiogenically supplied new vessels derived from host tissues permit tumors to grow exponentially. Retinoblastomas with increased angiogenesis have a greater potential for tumor progression, invasion of surrounding structures, and metastasis (19;20).
The degree of angiogenesis can be assessed by evaluating histopatholigical angiogenic markers such as microvessel density (MVD), or expression of vascular endothelial growth factor (VEGF) and its receptors. High tumor MVD in retinoblastoma is correlated to invasive growth and metastasis and is associated with a poor prognosis (19;20). VEGF is highly expressed in retinoblastoma, and in addition to promoting angiogenesis, VEGF causes an increased vascular permeability in neovascular capillary beds with subsequent blood-ocular barrier (BOB) breakdown (21-23). VEGF released in the posterior eye segment is able to diffuse into the aqueous of the anterior chamber, where it can induce iris angiogenesis (clinically known as 'rubeosis iridis'), spatially separated from the tumor location (22-26). In iris angiogenesis a membrane

of new vessels forms across the iris and anterior chamber angle, eventually causing secondary (angle closure) glaucoma. Retinoblastoma associated iris angiogenesis, for which enucleation is usually performed, is considered a bad prognostic factor for globe salvage and vision.

The study described in **chapter 4.1** showed an abnormal anterior eye segment (AES) contrast enhancement in 35% (20/57 eyes), which could be explained in the majority of these patients by the clinical presence of hyperemia (six eyes), uveitis (one eye), and iris angiogenesis (rubeosis iridis) (eight eyes). The histopathological specimen of some of these eyes showed an increased number of vessels in the iris, suggesting iris angiogenesis. Galluzzi et al. had already shown a significant correlation between histopathologically documented optic nerve and/or choroid infiltration and abnormal AES enhancement. This parameter seemed to be an indicator of more aggressive behavior of retinoblastoma. However, no histopathological substrate for this abnormal enhancement was found. In **chapter 5.1** we investigated the histopathologic basis of abnormal AES enhancement in a group of 42 patients using a 3-point score. The degree of abnormal AES enhancement was moderate in 15 (36%) eyes and strong in 14 (33%) eyes. Only 13 (31%) eyes showed normal AES enhancement. In a multivariate analysis, the degree of AES enhancement showed statistically significant correlations with iris surface-vessel count (P = .05) and optic nerve invasion (P = .04) in the enucleated eye and with tumor volume (P = .02) as detected on MR imaging. No significant associations between AES enhancement and VEGF expression in the iris were observed. However, Flt-1 (VEGF-receptor-1) (P = .04) staining in iris stroma and iris angiogenesis as detected with CD31 staining (P = .009) both yielded a statistically significant positive correlation with abnormal AES enhancement. We concluded that AES enhancement is a hallmark of advanced retinoblastoma because the degree of AES enhancement correlates with tumor volume and optic nerve invasion.

The degree of abnormal AES enhancement on MR imaging in retinoblastoma reflects angiogenesis in the iris, spatially separated from the tumor. Dynamic contrast-enhanced (DCE) MRI represents the acquisition of serial MR images before, during and after the administration of an intravenous contrast agent. In **chapter 5.2**, the potential of dynamic contrast enhanced (DCE) MRI for assessment of tumor angiogenesis and vitality was evaluated in a group of 15 retinoblastoma patients. Using the curve-pattern analysis method for analysis of tumor enhancement, the early phase of the DCE time curve (κ_{5min}) positively correlated with tumor MVD (P = .008). For the full time series (17min) κ correlated negatively with the degree of tumor necrosis (P = .002). Metastatic risk factors (optic nerve and choroid invasion) and presence of VEGF did not show a significant correlation with DCE kinetic data. This analysis suggests that

DCE-MRI with curve-pattern analysis is a feasible, non-invasive way to assess tumor angiogenesis and degree of necrosis in retinoblastoma.

Diffusion-weighted (DW) MRI, an MRI technique initially used for detection of cerebral ischemia and infarction, has been increasingly used extracranially to characterize soft tissue masses. DWI represents the diffusion behavior of water in tissue and is characterized by the apparent diffusion coefficient (ADC). Several studies and case series have used DWI to characterize head and neck and orbital masses and monitor treatment response by serial ADC measurements (27-32). Retinoblastoma may exhibit variable hyperintensities on DW images, resulting in different values in the ADC-maps, depending on their histology and cellularity. However, echo-planar (EP)-based DWI suffers from susceptibility artifacts and image distortions, which makes DWI of the orbit a challenging technique. The aim of the study, described in **chapter 5.3**, was to investigate the feasibility of single-shot turbo spin-echo (HASTE) DWI in the evaluation of children with retinoblastoma and to assess the value of ADC-maps in differentiating between viable and necrotic tumor tissue. In 17 patients with retinoblastoma, non-EP DWI was performed by using a HASTE-sequence with *b-values* of 0 and 1000 s/mm^2. ADC-values were measured for enhancing and nonenhancing tumor tissue and compared with histopathologic findings regarding tumor differentiation and viability. On DWI (b=1000 s/mm^2), vital tumor tissue showed hyperintensity with negligible intensity of surrounding vitreous. We found a statistically significant difference ($P < .0005$) in mean ADC-values between enhancing and nonenhancing tumor parts of retinoblastoma. Histopathologically, low ADC-values (enhancing tumor parts) correlated to viable tumor tissue, whereas intermediate ADC-values (nonenhancing tumor parts) correlated to necrotic tumor tissue. HASTE DWI enabled adequate characterization of retinoblastoma. ADC is a helpful tool to differentiate between viable and necrotic tumor tissue and might be valuable to monitor response to eye-preserving therapies.

CLINICAL IMPLICATIONS

Ocular masses in children represent a spectrum of benign and malignant lesions that can be challenging to diagnose and treat. Although most retinoblastoma patients are diagnosed by fundoscopy and ultrasound, MR imaging studies should be performed in all patients to help confirm the diagnosis and to determine extent of disease (extraocular spread or trilateral retinoblastoma).

The use of eye size as an additional parameter to differentiate between retinoblastoma and (benign) simulating lesions should be considered carefully. As we describe in

chapter 3.1, a small size of the affected eye should not be used as a criterion to exclude retinoblastoma or to favor a diagnosis of retinoblastoma-simulating lesions. Eyes affected by retinoblastoma are usually smaller compared to normal eyes.
MRI is the most powerful tool for imaging the globe due to the excellent tissue contrast it provides. Currently, imaging of ocular neoplasms and simulating lesions has shifted towards baseline MRI and there is no additional role for CT in retinoblastoma. The results described in this thesis, which are confirmed in the literature, show clear evidence that MRI is the most accurate diagnostic tool in staging retinoblastoma (5-7;33-35). However, radiologists involved in (pediatric) ocular MRI should realize that diagnostic accuracy of this technique depends on the optimization of the scanning protocol (hardware and software), with appropriate spatial resolution. From a basic technical point of view, it is not possible to assess details measuring less than 1 mm with routine MRI protocols. In **chapter 2.1**, recommendations were formulated for imaging retinoblastoma on the basis of evidence and expert consensus. To reach an appropriate imaging resolution (≤ 0.5 x 0.5 mm in-plane pixel size) in 1.5-Tesla machines the use of small surface coils is mandatory. With the current 3-Tesla MRI options, imaging with a head coil has vastly improved, and the available multi-channel array head coils (32-channel coil) result in high quality diagnostic images with the required high spatial resolution.

In **chapter 2, 4 and 5** of this thesis imaging criteria to assess extent of intraocular disease and presence of optic nerve or extraocular extension on postcontrast T1-weighted images were formulated:

- Choroidal invasion: localized thickening and heterogeneous contrast enhancement near tumor (interruption of linear enhancing choroid)
- Scleral invasion: interruption of thin hypointense layer surrounding the enhancing choroid
- Optic nerve invasion: thickening of optic disk or interruption of linear enhancement of the choroidoretinal complex (prelaminar); enhancement of the distal nerve, posterior to the virtual line joining the scleral margins of the lamina cribrosa (postlaminar invasion).

We conclude that despite an overall good performance of MRI for detection of tumor extent, there is room for improvement. Diagnostic accuracy for detection of risk factors seems high, but data may be inaccurate due to its relatively low prevalence (postlaminar invasion, massive choroidal and scleral invasion). This is confirmed by other published series in the literature in which the calculated 95% confidence intervals are still very large (6;33).

Besides direct detection of metastatic risk factors on MRI, we also attempted to identify indirect signs for advanced disease. We found that tumor volume is strongly associated with choroidal invasion and optic nerve invasion, but only with prelaminar optic nerve invasion. The absence of an association with postlaminar invasion is likely to be the result of its low prevalence in our study. Brisse et al. in a more recent study, describe a statistically significant association between tumor size and postlaminar optic nerve invasion in a large patient population (33).
In this thesis the association between abnormal enhancement in the AES and metastatic risk factors was also studied. Our study results indicate that abnormal AES enhancement is a hallmark of advanced retinoblastoma because its degree correlates with tumor volume and optic nerve invasion. Radiologists should be aware of this sign since it represents a degree of iris angiogenesis, which is a bad prognostic factor for globe salvage.
Routine ophthalmoscopy has a low sensitivity for detecting early or subtle stages of iris angiogenesis, a finding confirmed in our study (two eyes with iris angiogenesis detected clinically, compared with 14 eyes detected histopathologically) (36;37). The degree of AES enhancement might be a valuable diagnostic parameter in the choice between enucleation and conservative treatment strategies. Normal AES enhancement seems to be an indication for considering globe salvage rather than enucleation. Abnormal AES enhancement, especially in eyes showing a strong enhancement, represents a sign of iris angiogenesis and could be considered an additional argument in favor of enucleation.

Brain MRI should be systematically performed in all new retinoblastoma patients to depict possible associated midline CNS tumors or CNS malformations. Although pineal cysts are infrequent in the young population - these lesions may occur in retinoblastoma patients. Radiologists should be aware of these lesions since small pineoblastomas can present with central necrosis. On the other hand, pineal cysts can show an atypical MRI appearance, including large size and nodular irregular enhancement, which overlaps with the appearance of pineoblastoma and may lead to an incorrect diagnosis.
The European Retinoblastoma Imaging Collaboration therefore recommends brain MRI in all new retinoblastoma patients and follow-up MRI for pineal cysts:

- Normal pineal gland at baseline: no further follow-up
- Simple pineal cyst: follow-up MRI once within 1 year (6-12 months). If stable, no further follow up
- Complicated pineal cyst: follow-up MRI within 3 months. If stable, no further follow up. If any doubt persists, another follow-up after 3 months.

A multicenter prospective study is needed to validate these recommendations, which might lead to early identification of pineoblastoma and most likely a better survival.

THE FUTURE OF IMAGING IN RETINOBLASTOMA

The field of radiology never gets old. The way in which we image various disease entities continually evolves and improves. With the implementation of high-field MR systems and new coils, an important increase in image resolution can be achieved. Advanced MR imaging sequences such as DW and DCE MRI yield the possibility to non-invasively characterize tissues and depict structural changes at a cellular level. Important goals in retinoblastoma imaging in the near future are to further improve its capabilities as problem-solving tool in leukocoria, to further increase diagnostic accuracy in staging local and regional disease extent, and to monitor tumor response to conservative treatment.

Diagnosis

Detection of calcification is critical for the diagnosis of retinoblastoma. Galluzzi et al, showed that gradient-echo T2*-weighted MRI might be a feasible technique to detect intraocular calcifications (38). Diagnostic accuracy of this technique needs to be determined in a future study in which in-vivo obtained T2*-weighted images are compared to ex-vivo CT-images of the enucleated eye and histopathology. Furthermore, DW MRI may potentially aid in differentiating between malignant and benign lesions. Quantitative measurements of ADC can be an indicator of malignancy in intraocular lesions, with low ADC values in malignant lesions compared with benign lesions. This could theoretically help to differentiate retinoblastoma from Coats disease, as we would expect a much higher ADC with the hypocellular, exudative retinopathy as seen in Coats disease. A future multicenter ERIC study could resolve this, since both diseases are uncommon.

Staging

With the introduction of a standardized protocol for high-resolution MR imaging of retinoblastoma, the accuracy of MRI for the diagnosis of metastatic risk factors may still further improve. Recently, a multicenter prospective study was undertaken with MR images and histopathological results from different centers participating in ERIC, with the goal to determine diagnostic accuracy of this high-resolution protocol in a large patient group. Optimal MRI criteria for detecting metastatic risk factors should be defined (i.e. measurements of the extent of abnormal enhancement in the distal portion of the optic nerve). It would be interesting to investigate if baseline MRI screening of the brain with extended follow-up of simple and complicated pineal cysts

is effective in early diagnosis of pineoblastoma, and to evaluate whether this would reduce mortality.

Conservative treatment and response evaluation

Intravenous chemotherapy combined with local consolidation has shifted management of retinoblastoma in favor of globe salvage, since successful tumor control can be achieved in most small and some advanced tumors. However, systemic chemotherapy frequently causes severe toxic side effects. As a result, newer treatment approaches have involved localized administration of chemotherapy to minimize systemic side effects. The most recent development is selective intra-ophthalmic artery infusion of the chemotherapeutic drug Melphalan during a neurointerventional procedure, which shows promising results regarding tumor control. However, some children in both systemic intravenous chemotherapy and selective intra-arterial chemotherapy treatment strategies still end up with enucleation due to tumor progression.

The big future challenge for imaging in retinoblastoma will be to non-invasively characterize the intraocular tumor by means of advanced imaging techniques (DW- and DCE-MRI), and therefore help to recognize patients suitable for conservative treatment and to provide biomarkers for early detection of treatment response. The preliminary results on DW- and DCE-MRI indicate that with these techniques, parameters such as tumor vitality, necrosis and angiogenesis can be detected. Before these techniques can be applied in prospective studies for response evaluation, the DW- and DCE-MRI acquisition protocols and images analysis methods should be standardized between retinoblastoma centers.

New developments in Retinoblastoma Imaging

Optical Coherence Tomography (OCT) is a non-invasive optical technique analogous to ultrasound that can create high-resolution cross sectional images of the human retina. OCT provides an improved resolution to detect very small tumors at an earlier, possibly intra-retinal stage (39). Children with a positive family history for retinoblastoma are screened periodically during examinations under general anesthesia from birth to survey for new tumors. With the development of OCT systems that can be used in the operating room during examinations under anesthesia, detection of very early (intra-retinal) stages of retinoblastoma becomes possible. Intra-operative OCT imaging is an exciting new technology that may improve the diagnosis and management of retinoblastoma tumors. Major advances in studying early stage disease, detecting vital tumor tissue and predicting response the conservative treatment are furthermore to be expected from combining OCT with other imaging modalities (ultrasound, MRI, autofluorescence imaging).

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